IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Y. BYUN et al.	
FOR:	AMPHIPHILIC POLY-SACCHARIDE DERIVATIVES	
SERIAL NO.:	09/300,173	
FILED:	April 27, 1999	**DECLARATION UNDER 37 C.F.R. § 1.132**
EXAMINER:	K. Fonda	
ART UNIT:	1623	
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Commissioner for Patents
Washington, D.C., 20231

DECLARATION OF YOUNGRO BYUN, Ph.D.:

YOUNGRO BYUN, Ph.D. hereby declares as follows:

1. That he is a coinventor of the invention described and claimed in the above-identified application ("application") filed on April 27, 1999, as Serial No. 09/300,173.

CERTIFICATE OF DEPOSIT UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on November 15, 2000.

Respectfully submitted,

Alan J. Howarth

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2. That he is an Assistant Professor at Kwangju Institute of Science & Technology, Kwangju, Korea.

3. That he conducted experiments for comparing the oral absorptions of a heparin-deoxycholic acid conjugate ("heparin-DOCA"), a heparin-cholesterol conjugate, and a heparin-cholic acid conjugate, which are described herein.

4. That heparin-DOCA was synthesized according to the procedure of Example 1 of the application, and heparin-cholesterol was synthesized according to the procedure of Example 2 of the application.

5. That heparin-cholic acid was synthesized according to the procedure of Example 1 of the application except that cholic acid was substituted for DOCA, and the heparin derivatives prepared according to this procedure were tested by FT-IR and ^{3}H-NMR, these tests showing the presence of a new amide bond, which proved that a heparin-cholic acid conjugate was formed by coupling of an amine group of heparin with a carboxyl group of cholic acid (see band at 1585 cm^{-1} in FIG. 1 attached hereto).

6. That Sprague-Dawley rats housed at the animal care facility of the Korea Animal Center were fasted for 12 hours before dosing, groups of rats weighing 250-300 g were administered a single oral dose of heparin-DOCA, heparin-cholesterol, or heparin-cholic acid at 100 mg/kg, then blood samples (0.5 ml) were collected serially by a heparin-coated capillary and mixed with 3.8% sodium citrate, samples being collected prior to administration of the heparin derivatives and for 10 hours thereafter at hourly intervals, the plasma being harvested by centrifugation and frozen at -20°C, then heparin activity in each sample being determined by APTT assay.

7. That the clotting time for normal plasma (without heparin) is about 18 seconds, but the heparin-DOCA, heparin-cholesterol, and heparin-cholic acid

all incr as d clotting time, the maximum clotting times being 39.3 7 13.3 seconds for heparin-DOCA, 32 7 32.61 seconds for heparin-cholesterol, and 28.7 7 3.0 seconds for heparin-cholic acid (see FIG. 2).

8. That these results show that oral absorption of heparin-DOCA exceeded that of heparin-cholesterol, which in turn exceed that of heparin-cholic acid, showing that heparin-DOCA is substantially more suitable for oral absorption of hydrophobized heparin than heparin-cholic acid, which result is unexpected and surprising.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Date: NOV. 13. 2000

Youngro Byun, Ph. D.